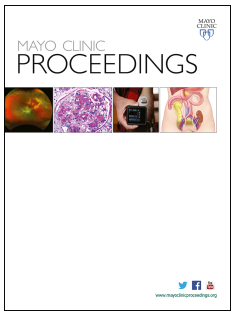
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof



Clinical Benefit of Lenzilumab in Cases of Coronavirus Disease 2019

Andrea Aroldi, MD, Roberto Chiarle, MD, Carlo Gambacorti-Passerini, MD

PII: S0025-6196(21)00006-9

DOI: https://doi.org/10.1016/j.mayocp.2020.12.030

Reference: JMCP 3280

To appear in: *Mayo Clinic Proceedings*

Received Date: 23 November 2020

Accepted Date: 23 December 2020

Please cite this article as: Aroldi A, Chiarle R, Gambacorti-Passerini C, Clinical Benefit of Lenzilumab in Cases of Coronavirus Disease 2019, *Mayo Clinic Proceedings* (2021), doi: https://doi.org/10.1016/j.mayocp.2020.12.030.

Clinical Benefit of Lenzilumab in Cases of Coronavirus Disease 2019

Andrea Aroldi, MD (Corresponding author)
Hematology Division and Clinical Research Unit,
San Gerardo Hospital, Monza, Italy.
Department of Medicine and Surgery,
University of Milano-Bicocca,
Monza, Italy.

andrea.aroldi@unimib.it

Roberto Chiarle, MD
Department of Pathology,
Children's Hospital Boston and Harvard Medical School,
Boston, MA, USA.
Department of Molecular Biotechnology and Health Sciences,
University of Torino,
Torino, Italy.

Carlo Gambacorti-Passerini, MD
Hematology Division and Clinical Research Unit,
San Gerardo Hospital,
Monza, Italy.
Department of Medicine and Surgery,
University of Milano-Bicocca,
Monza, Italy.

Letter to the Editor

Clinical Benefit of Lenzilumab in Cases of Coronavirus Disease 2019

To the Editor: Temesgen et al[1] carefully depicted the clinical benefit provided by Lenzilumab in cases of coronavirus disease 2019 (COVID-19), sustained by the novel severe acute respiratory coronavirus 2 (SARS-CoV-2), where cytokine storm may lead to fatal multi-organ failure. Lymphopenia is a typical finding occurring at early onset of the disease and Lenzilumab administration showed a significant improvement in terms of lymphocyte count, which has not been fully understood by the Authors, suggesting that granulocyte-monocyte colony-stimulating factor (GM-CSF) might have a direct impact on T cells.

SARS-CoV-2 related hyperinflammatory pattern resembles the cytokine release syndrome (CRS) occurring in Chimeric Antigen Receptor (CAR) T cell therapy, where host monocyte-macrophage system is the major source of cytokine production (e.g. interleukin (IL)-1 and IL-6).[2] In this setting, Lenzilumab showed to be effective in reducing CAR T-mediated CRS and neuroinflammation at the same time, enhancing adoptive T cell therapy as well.[3]

Previous preclinical data in SARS-CoV infected mice showed that inflammatory monocyte-macrophage response, secondary to dysregulated type-I interferon activity during SARS-CoV infection, results in lethal pneumonia and cytokine-induced apoptosis of T cells (specifically mediated by tumor necrosis factor alpha – TNF-α).[4]

As already known, GM-CSF inhibition turned out to broadly modulate monocyte-macrophage activity by simultaneously reducing a spectrum of inflammatory cytokines, including TNF-α.[3] We therefore suggest that the direct regulation of monocyte-macrophage activity by Lenzilumab, with subsequent broad cytokines shutdown, could provide a more favorable micro-environment where effector T cells could also be protected from cytokine-induced apoptosis. This would preserve a non-exhausted T cell phenotype, being more effective against infections and performing more potently T cell specific antiviral immunity to achieve viral clearance.

Aware of the good safety profile of Lenzilumab in this current study and previous analysis,[1,5] the treatment is feasible and safe and the ongoing randomized phase III trial (NCT04351152) will extensively confirm the lymphocyte recovery in Sars-CoV-2 infection and the impact of the drug on COVID-19 clinical improvement.

Andrea Aroldi, MD
San Gerardo Hospital
University of Milano-Bicocca
Monza, Italy

Roberto Chiarle, MD
Children's Hospital Boston and Harvard Medical School,
Boston, Massachusetts
University of Torino
Torino, Italy

Carlo Gambacorti-Passerini, MD
San Gerardo Hospital
University of Milano-Bicocca,
Monza, Italy

References

1. Temesgen Z, Assi M, Shweta FNU, et al. GM-CSF Neutralization With Lenzilumab in Severe COVID-19 Pneumonia: A Case-Cohort Study. *Mayo Clin Proc*. 2020;95(11):2382-2394.

2. Agarwal S, June CH. Harnessing CAR T-cell Insights to Develop Treatments for Hyperinflammatory Responses in Patients with COVID-19. *Cancer Discov*. 2020;10(6):775-778.

3. Sterner RM, Sakemura R, Cox JC, et al. GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. *Blood*. 2019;133(7):697-709.

4. Channappanavar R, Fehr AR, Rahul Vijay R, et al. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell Host Microbe*. 2016;19(2):181-93.

5. Patnaik MM, Sallman DA, Mangaonkar AA, et al. Phase 1 study of lenzilumab, a recombinant anti-human GM-CSF antibody, for chronic myelomonocytic leukemia. *Blood*. 2020;136(7):909-913.